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Motor unit firing patterns during sustained ischemic submaximal contractions

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Motor unit firing patterns during sustained ischemic submaximal contractions

by

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Dedication

I would like to dedicate my thesis to my husband and my parents. Without their love and support, I would not be where I am today.

Acknowledgements

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Abstract

Motor unit firing patterns during sustained ischemic submaximal contractions

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The aim of this study was to determine motor unit firing patterns during ischemic versus non-ischemic sustained submaximal isometric contractions of the tibialis anterior muscle. 10 healthy adults attended two experimental sessions approximately 48 hours apart. Both sessions were identical except that the fatigue task in one was performed with a pressure cuff placed above the knee and inflated to 180 mm Hg. Three 5s maximum voluntary contractions (MVCs) were performed prior to and after the fatigue task. Each participant held a target force of 20% MVC until endurance time (peak-to-peak tremor amplitude exceeded 5% MVC). Single motor unit firing rates (11 non ischemic, 9 ischemic) were recorded with intramuscular fine wire electrodes. Mean interspike intervals over 5s time bins were calculated at every 5% endurance time. The endurance time for the ischemic (3.7 ± 0.58 min) fatigue task was significantly ($p<0.001$) shorter than the non-ischemic (9.5 ± 0.57 min) task. There was no significant difference in mean motor unit firing rates between the two conditions ($p=0.883$). Within both tests, there was a significant decline in firing rate (ischemic initial: 12.95 ± 0.71 Hz, minimum: 11.41 ±

0.81 Hz, p=0.023; non-ischemic initial: 13.13 ± 0.87 Hz, minimum: 11.15 ± 0.48 Hz, p=0.012). The time to minimum firing rate was significantly ($p<0.001$) less in the ischemic (1.29 ± 0.2 min) compared to non-ischemic (3.14 ± 0.23 min) condition. Muscle ischemia significantly reduced endurance time and the time to minimum firing rate. However, there were no differences in average motor unit firing rates between the two conditions across the relative phases of endurance time.

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CHAPTER I: Introduction

Diverse results exist regarding the firing patterns of motor units during submaximal fatiguing contractions. Several studies have measured motor unit firing patterns during maximum and submaximal voluntary contractions. Different outcomes have been reported due to variation in protocols, level of contractions and muscles investigated. However, not much has been studied about firing patterns during sustained ischemic submaximal fatiguing contractions.

During maximum voluntary contractions motor unit firing rates decrease (Grimby et al. 1981; Bigland-Ritchie et al. 1983; Marsden et al. 1983; Gandevia et al. 1990). This has been likely due to decreased central drive (Gandevia et al. 2001; Taylor and Gandevia 2008). During sustained submaximal contractions, a decline in the motor unit firing rates have been observed in biceps brachii (Garland et al. 1994; Ivanova 1990), triceps (Garland et al. 1997), thenar muscles (Gatev et al. 1986) and deltoid (De Luca and Forrest 1973). Some of the recent studies have shown a decline followed by a late increase in firing rates during submaximal contractions (Griffin et al. 2000, Adam and De Luca 2005). During intermittent submaximal contractions, a decrease in the firing rates have been observed in biceps (Christova and Kossev 1998) where as an increase in firing rates was shown for quadriceps (Bigland-Ritchie et al. 1986; Maton and Gamet 1989). A triphasic pattern in biceps brachii during submaximal contractions was also investigated (Dorfman et al. 1990). The mechanism by which central nervous system behaves in submaximal fatigue is not well understood. It is extremely difficult to draw a conclusion regarding the trend of firing patterns during submaximal contractions.

Ischemia during fatigue in the active muscle tissue can inhibit cortical excitability (Taylor and Gandevia 2008). No recovery of firing rates was observed during 3 min of rest after MVC if the fatigue muscle was kept ischemic (Bigland-Ritchie et al. 1986; Woods et al. 1987). A decrease in H-reflex amplitude was reported in the soleus muscle during ischemia (Garland and Mc Comas 1990). This was attributed to existence of reflex inhibition during fatigue (Garland 1991). However, significantly higher motor unit firing rates were observed during ischemic intermittent submaximal (20% MVC) contractions in humans (Moritani et al.1992). But the motor unit firing frequencies in that study were calculated from the entire population of motor units which may have differed before and after fatigue. Thus it is not known how ischemia will affect the firing rates of motor units active from the onset of a sustained contraction.

The purpose of this study was to investigate single motor unit firing patterns during ischemic sustained submaximal contractions of the tibialis anterior muscle in able bodied individuals.

CHAPTER II: Materials and Methods

Participants

5 males and 5 females (Mean ± SE: 24.8 ± 1.47 yrs) with no history of neurological or metabolic disorder or injury to the right leg participated in this study. Participants attended two experimental sessions that lasted for approximately one hour each. N = 20 motor units (11 non-ischemic, 9 ischemic) were recorded with intramuscular fine-wire electrodes. Participants were recruited from the University campus by flyers. All individuals attended an orientation session prior to participating in the experiment. During that time they were familiarized with the experimental arrangement and signed an informed consent approved by The University of Texas at Austin Internal Review Board. They also practiced performing MVCs and holding isometric contractions. Both test days were identical except that the fatigue task in one was performed under ischemic condition. The order of experiments was randomized and separated by at least 48 hours to allow for recovery from fatigue.

Experimental Setup

Participants were seated in an adjustable chair with the right knee and ankle fixed at 90º and the foot strapped to a metal plate. The right knee and ankle joints were immobilized with pads and straps above and below the knee joint, and the right foot was strapped to an aluminum plate attached to a strain gauge. The experimental arrangement is shown in Figure 1. Participants were provided with visual feedback of the force on a computer screen positioned in front of them.

The area of electrode placement was first shaved and cleaned with 70% isopropyl alcohol. Intramuscular insulated stainless steel fine-wire (0.002 mm) electrodes (California Fine Wire Company, Grover Beach, CA) made of three fine-wires were used to record single motor unit data. Each of the fine-wire electrodes was made of three wires; one was used as the active electrode, another as the reference, and the third was used as a spare. The intramuscular electrodes were then inserted with a thin hollow needle (25g) just under the skin and into the muscle belly of tibialis anterior muscle of right leg. A ground electrode was placed over the medial malleolus.

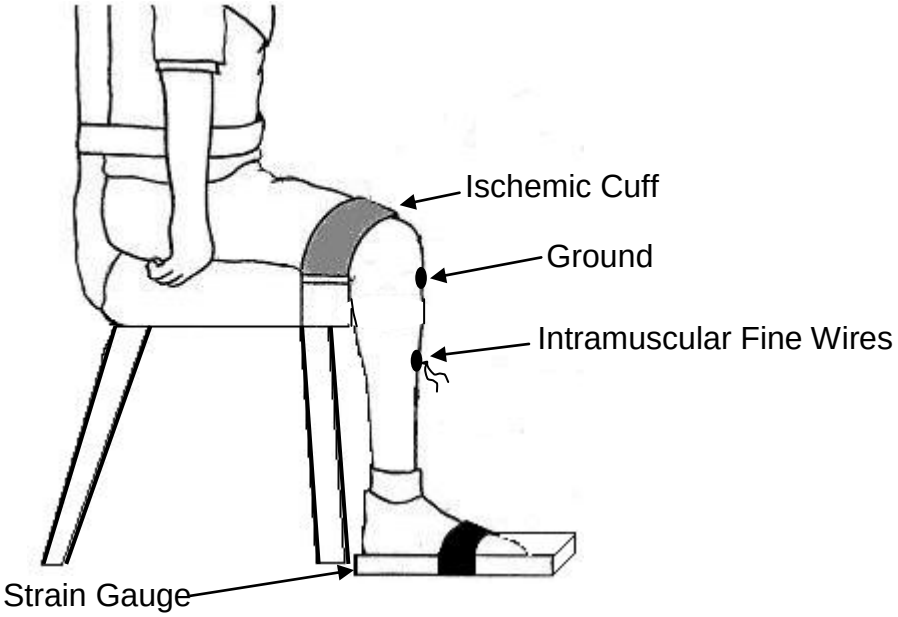

Figure 1: Experimental arrangement. Position of the participant with knee and foot flexed 90 degrees and the site of insertion of intramuscular fine wire electrode

Experimental Protocol

Three 5s MVCs with 10s of rest in between were performed prior to insertion of the EMG electrodes. The average of the three MVCs was used to determine the target forces for the remaining voluntary contractions. Participants were instructed to perform

the MVCs as fast and forcefully as possible and were provided with verbal encouragement during the performance of MVCs

After the fine-wire electrode was inserted, participants performed the fatigue task which consisted of holding a 20% MVC isometrically until the endurance limit. The endurance limit was defined as peak-to-peak tremor amplitude exceeding 5% MVC. For the ischemic condition, a pressure cuff was placed above the knee and inflated to 180 mm Hg for the duration of the fatigue task. To ensure that the muscle is ischemic, blood flow in the posterior tibial artery between the medial maleolus of the tibia and the medial tubercle of the calcaneum was monitored using Doppler ultrasound as shown in figure 2 (8 MHz, model 810-A, Parks Medical Electronics Inc. Aloha, USA).

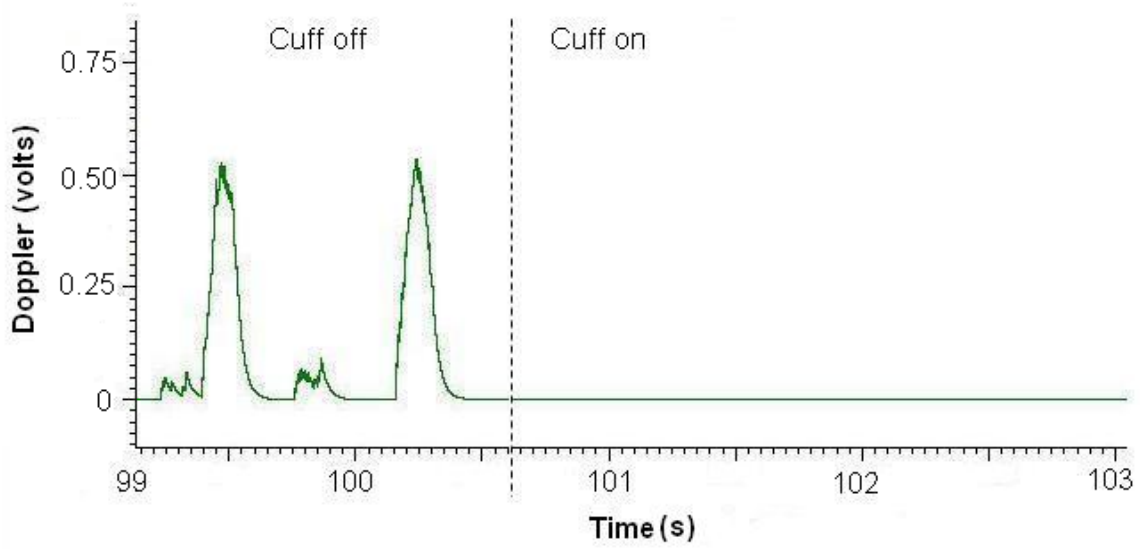

Figure 2: Recording from Doppler. The audio signals from the Doppler were converted to visual signals. The blood flow is indicated by the initial waves, however a flat line afterwards indicates that the blood flow was occluded

Data Analysis

The dorsiflexor force output signal was measured by a load cell attached to a metal plate, amplified, and analogue to digital converted. Intramuscular EMG was pre-amplified, bandwidth filtered 10 Hz-3.12 kHz with a gain of 330 (B&L Engineering, Tustin, CA). The force and intramuscular EMG were digitized at 1,000 and 20,000 Hz, respectively (Micro 1401 Analog-Digital Converter, Cambridge Electronics Design (CED), Cambridge, UK). Dual monitors provided displays of the target and actual forces as well as the intramuscular EMG recordings throughout data collection. All data were analyzed off-line using Spike2 for Windows (version 5) software package (CED, Cambridge, England). Individual motor unit potentials were analyzed off-line with the Spike 2 waveform discrimination system (CED, Cambridge, England).

Mean single motor unit firing frequency was measured off-line during 5s time bin every 5% of endurance time. The first 5% segment of the fatigue task represented the initial motor unit firing frequency, the last 5% segment of the fatigue task represented the final motor unit firing frequency, and the 5% segment with the lowest mean motor unit firing frequency represented the minimum motor unit firing frequency. During the fatigue task, a total of 20 motor units were recorded (11 non-ischemic, 9 ischemic). All short interspike intervals (ISIs) $\leq$ 20 ms and $\geq$ 200 ms were excluded from the analysis.

Statistical Analysis

Motor unit firing rates were normalized to the initial firing rates. A two way repeated ANOVA with post hoc analysis was used to compare motor unit firing rates between groups (non ischemic and ischemic) and over time. Motor unit firing rates were

normalized to the initial firing rates. Bonnferoni corrections were used for post hoc analysis of multiple comparisons.

A paired t-test was used to compare the endurance time and time to minimum firing rates between the two groups. A two way repeated ANOVA was also used to compare the force outcome (N) with factors: groups (non-ischemic and ischemic) and time (before and after fatigue task). To compare the discharge variability, a two way repeated measures was used with factors groups (non-ischemic and ischemic) and over time.

An alpha level $p \leq 0.05$ was accepted as the level of statistical significance for all tests. All data are reported as mean ± standard error.

CHAPTER III: Results

Endurance Time

Endurance time was significantly lower (p=0.001) in the ischemic condition (3.71 ± 0.58 min) than in the non-ischemic (9.11 ± 0.56 min) condition. The results are shown in figure 3.

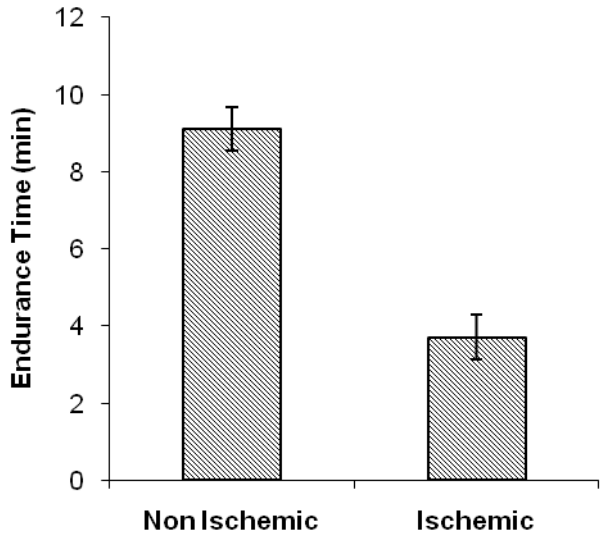

Figure 3: Difference in the endurance time (min) in both the groups (non-ischemic and ischemic). Significant reduction in endurance time for ischemic compare to non-ischemic. Error bars indicate the standard error

Time to minimum firing rate, as seen in Figure 4 was significantly (p=0.001) less in ischemic condition (1.29 ± 0.20 min) compared to non-ischemic (3.14 ± 0.23 min) condition.

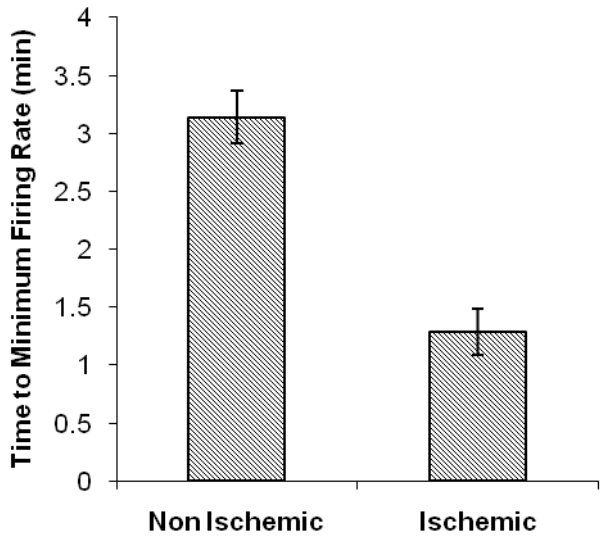

Figure 4: Difference in time to minimum firing rates in both the groups (non-ischemic and ischemic). Significantly shorter time to minimum firing rate in ischemic compare to non-ischemic condition. Error bars indicate the standard error

Maximum voluntary contractions

There was a significant decrease in post MVC force outcome as compared to pre MVC force in ischemic as well as non-ischemic condition (non-ischemic: pre 87.4 ± 10.7 N, post 67.4 ± 8.7 N , p=0.02 ; ischemic : pre 82.2 ± 11.6 N, post 54.8 ±8.8 N , p=0.01). However, there was no difference in post MVC force outcome between the groups (p=0.18).

Motor unit firing patterns

20 motor units were analyzed throughout the fatigue task, 11 in non-ischemic condition and 9 in ischemic condition. All the motor units were followed from the start until end of the fatigue task.

There was no significant difference in motor unit firing rate (% initial) between non-ischemic and ischemic conditions (p=0.883). The results are shown in Figure 5.

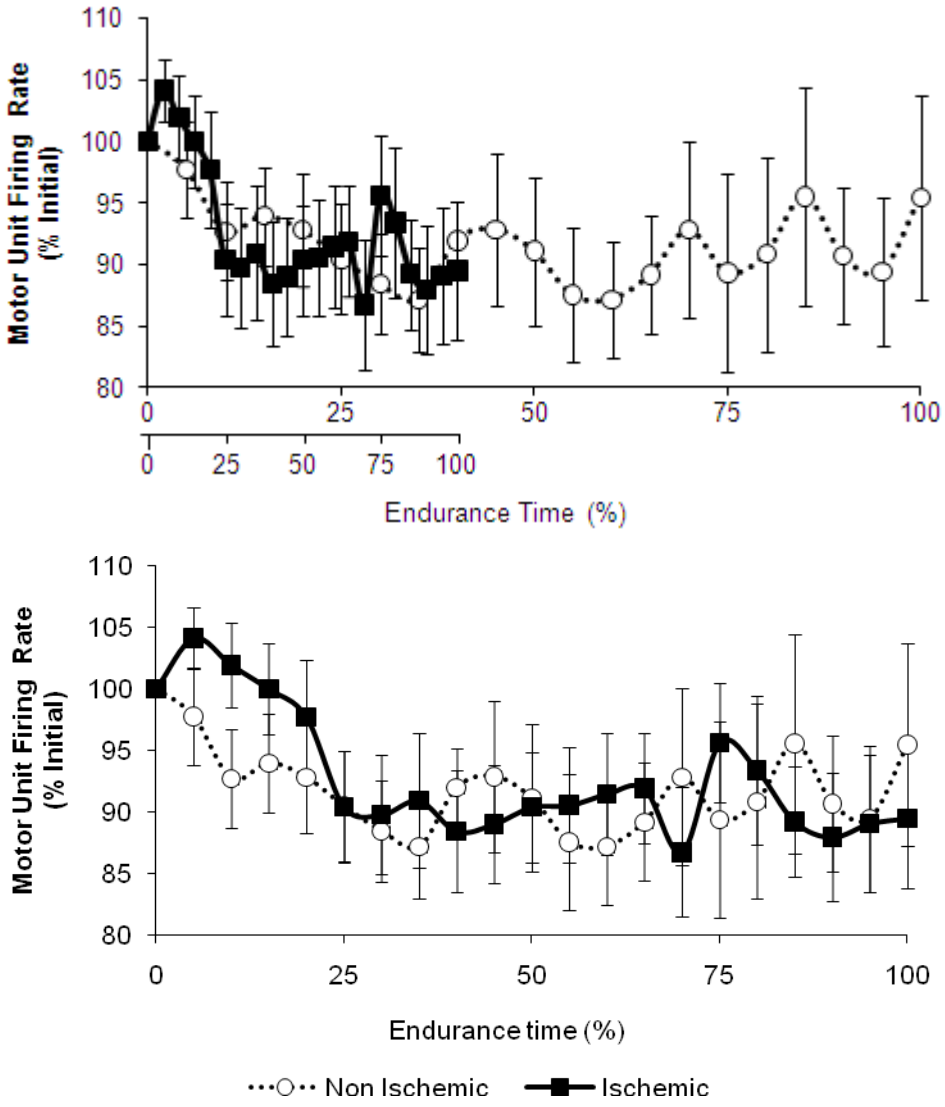

Figure 5: Mean motor unit firing rate (% initial) averaged over 5s bins every 5% endurance time (21 time bins) for ischemic and non-ischemic conditions. Each data point is the mean of all motor units analyzed. Error bars indicate the standard error

Motor unit firing rates during the initial, minimum and end of the fatigue task were also compared (Figure 6), and it was observed that there was a significant main effect for fatigue time ($p < 0.05$). Post hoc analysis revealed that initial firing rate (12.95 ± 0.71 Hz) was significantly higher than the minimum firing rate (11.41 ± 0.81 Hz, p=0.03) as well as final firing rate (11.43 ± 0.75 Hz, p=0.04) in ischemic condition. Initial firing rate (13.13 ± 0.87 Hz) was also higher (p=0.03) than minimum firing rate (11.15 ± 0.48 Hz) in non-ischemic condition. There was no significant interaction effect of group and endurance level.

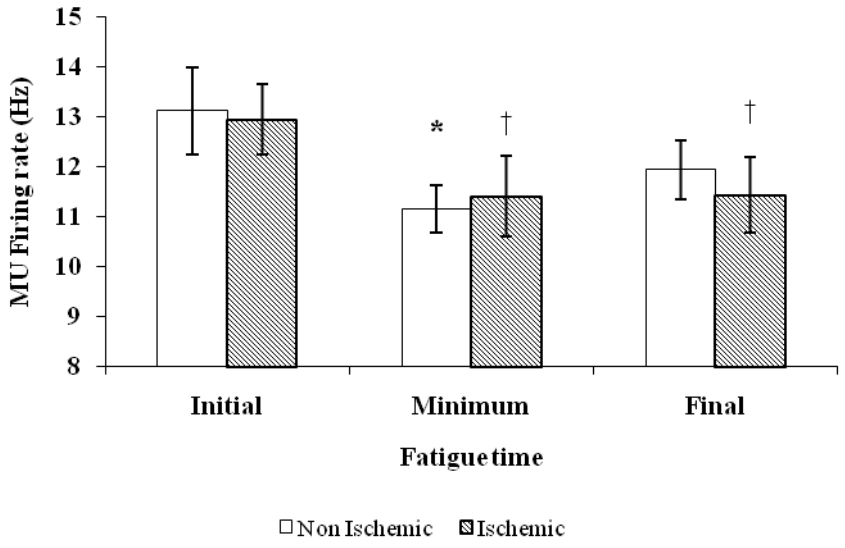

Figure 6: Mean initial, minimum and final motor unit firing rates for motor units analyzed throughout the fatigue task. * Indicates significantly lower motor unit firing rate than initial in non ischemic. † Indicates significantly lower motor unit firing rate than initial in ischemic. Error bars indicate the standard error

Best fit lines of all the single motor units recorded during non- ischemic and ischemic conditions were plotted. Most of motor units represent a decline in the firing rates compare to intial firing rates as seen in figure 7.

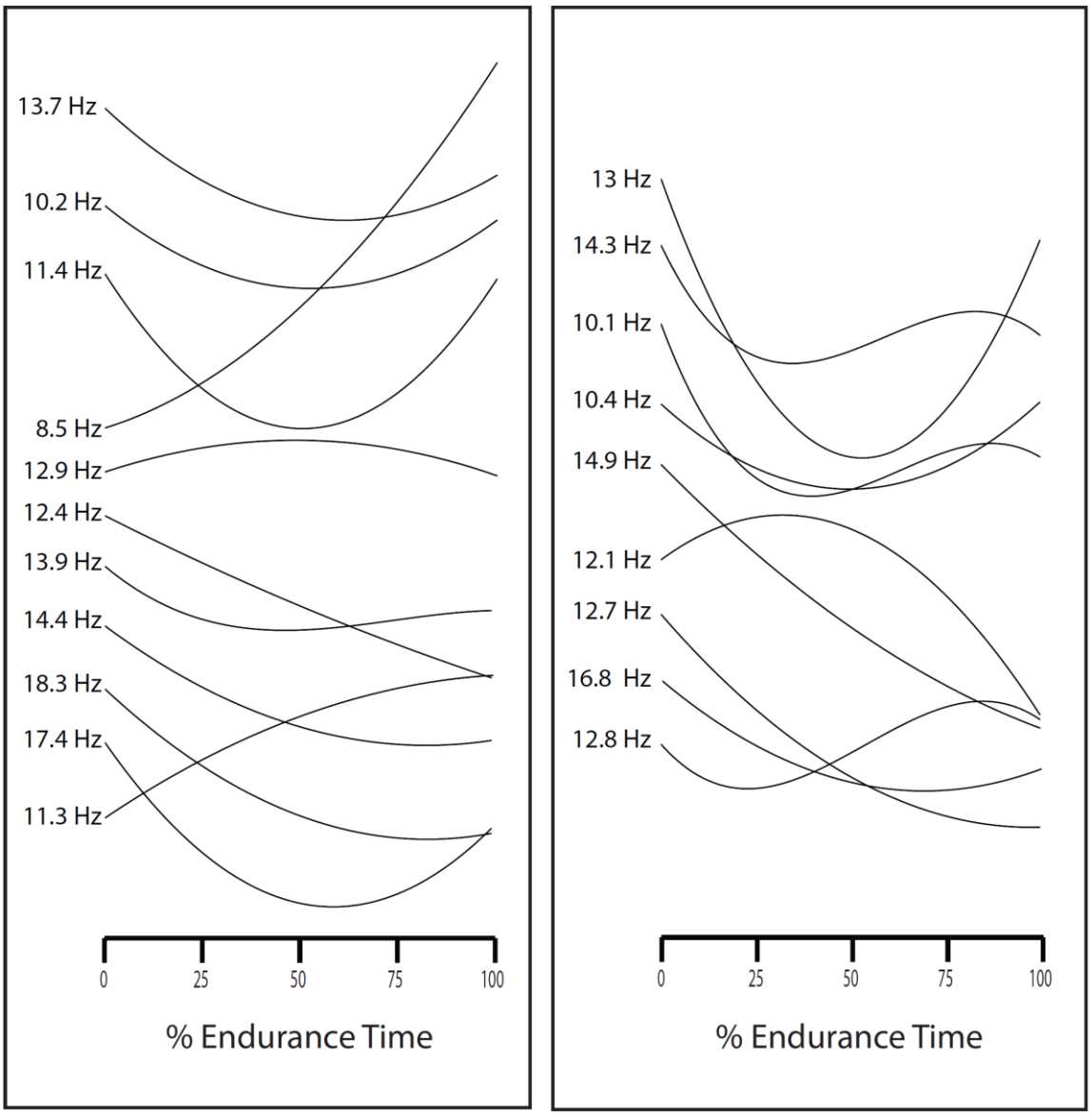

Figure 7: All single motor units plotted against endurance level. Best fit curves are represented. A) All the 11 non-ischemic motor units B) All the 9 ischemic motor units

Coefficient of variation

The coefficient of variation at 0% endurance level was significantly lower ($p<0.05$) than 75, 80, 85, 90, 95 and 100% endurance levels in the non-ischemic

condition. Similarly, under ischemic condition, coefficient of variation at 0% endurance level was significantly lower ($p<0.05$) than 80, 85, 90, 95 and 100% endurance levels (Figure 8). Over time, coefficient of variation increased in non-ischemic and ischemic condition. The coefficient of variation at 95 and 100% endurance levels were significantly higher in the ischemic condition than the non-ischemic condition (95% endurance time: non ischemic 15.1± 0.94 %, ischemic 19±1.04 %, $p=0.01$; at 100% endurance time: non ischemic 16.6±1.02 %, ischemic 20.3±1.25 %, $p=0.03$).

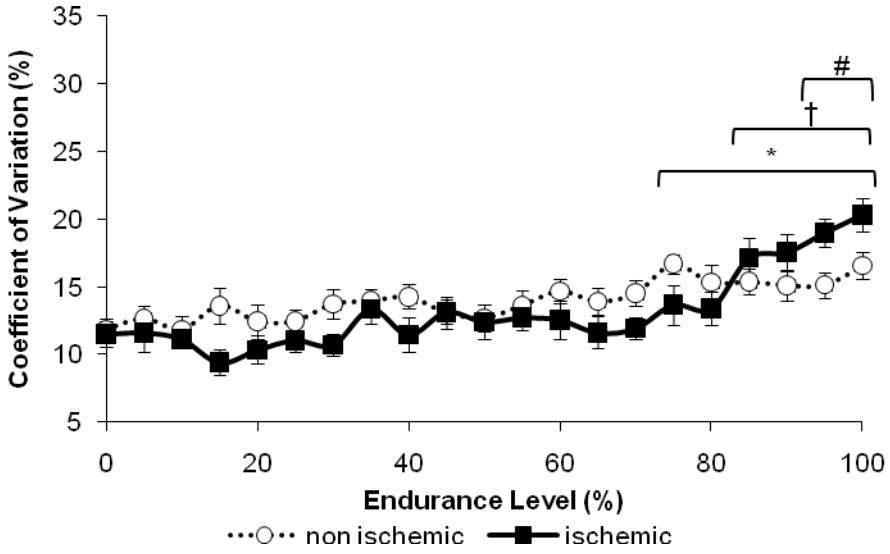

Figure 8: Discharge variability measured as SD/mean plotted against endurance time. * indicates difference in coefficient of variation from initial in non-ischemic group. † indicates difference in coefficient of variation from initial in ischemic condition. # indicates difference between two groups. Error bars indicate the standard error

CHAPTER IV: Discussions

The results indicate that endurance time and time to minimum firing rate were shorter during ischemic than non-ischemic submaximal fatiguing contractions. Motor unit firing rates declined over time in both the fatigue tasks. The firing patterns were similar for both the tasks. There was a reduction in MVC following the fatigue task. The coefficient of variation was higher at the end of the fatigue task than intial in both the condition. The discharge variability was different between the two conditions at the end of fatigue task.

The finding of a decline in motor unit firing rates was consistent with some of the previous studies (Person-Kudina 1972; Garland 1994; Garland 1997). This decline in motor unit firing rates during fatigue has been attributed to the muscle wisdom hypothesis (Marsden et al. 1983), twitch force potentiation (Klein et al. 2001), decreased central drive (Gandevia et al. 2001; Taylor et al. 2008), motor neuron adaptation (Kernel and Monster 1982; Spielmann et al. 1993), decrease in Ia afferent excitatory input to the motor neuron (Macefield et al. 1991), and inhibition from III and IV afferents (Bigland-Ritchie et al. 1983, Garland 1991).

There was no difference in the firing patterns between non-ischemic and ischemic conditions. In contrast to other studies where an increase in mean motor unit firing rates using 20% intermittent ischemic submaximal fatiguing contractions of hand muscles was observed (Moritani 1996), results from this study revealed no differences. The possibility of dissimilarity in the results could be due to the fact that this study examined a single motor unit pattern throughout the entire duration of the fatigue task, whereas past studies

usually reported the average firing rates of entire motor unit population. Single motor unit firing rates that declined during fatigue did not return to baseline when the muscle was held ischemic following a sustained maximal voluntary contraction (MVC) (Bigland-Ritchie et al.1986). However the fatigue mechanism may vary between maximum and submaximal voluntary contractions. In the maximum voluntary contractions all the motor units are activated while in submaximal voluntary contractions new motor units are recruited.

Adequate blood flow is required to transport oxygen to the exercising muscles (Anderson and Saltin, 1985). It is extremely essential to maintain oxygen supply and remove the metabolites formed to sustain submaximal exercise (Wernborn et al. 2006). Fatigue is quickly induced in hypoxic muscles (Fitts 1994) and also muscle ischemia leads to fatigue (Murthy et al. 2001). Fatigue is shown to be caused by central and peripheral factors. However, during an isometric sustained MVC, only 20% of fatigue developed is due to central factors while rest was due to accumulation of metabolites (Braun 1999). The accumulation of phosphate and protons during fatigue led to reduction in calcium sensitivity and a decline in maximal force (Allen et al 1992). While most studies have shown a correlation between muscle hypoxia and high intensity exercises (Eiken 1984), it is also shown that sustained contractions as low as 10% MVC reduces muscle oxygenation (Murthy 1997). Thus it can be inferred that because of accumulation of metabolites and inadequate oxygen supply, the fatigue process is rapid in ischemic condition, and hence supports the finding of this study where endurance time was very short under the ischemic condition as compare to the non-ischemic condition. However from the results of this study, it is unclear as to which metabolites might be playing a key

role in causing early fatigue in ischemia since no metabolites were measured in this study.

It was reported that acute ischemia reduces H/M ratio suggesting that acute ischemia has differential effects on sensory nerve propagation and synapse transmission (Zakuntansky 2005). H-reflex excitability has been observed to decrease in soleus muscle using electrically induced contractions and nerve blocks (Garland and Mc Comas 1990; Garland 1991). This decrease has been attributed to reflex inhibition from group III and IV afferents. The role of group III and IV afferent fibres of the lateral gastrocnemious muscle (LG) in modulating the homonymous monosynaptic reflex was investigated during muscle fatigue in rats. It was investigated that the presynaptic effect may be mediated by interneuron or may be due to a direct influence of group III and IV afferents on the large diameter afferents (Petorossi et al. 1999)

In studies on decerebrate cats, group III and IV afferent are stimulated by various metabolic products like lactic acid , arachdonic acid , bradykinin, etc. which may have accumulated during contractions (Rotto and Kaufman 1988; Mense 1977). The response of small diameter afferents of the cat triceps surae muscle is enhanced when blood flow is blocked by an ischemic cuff (Mense and Stanke 1983). This suggests that during muscular contraction, and particularly in ischemia, there is an accumulation of metabolites, and group III and IV afferents respond to this metabolic accumulation. Results from studies (Bigland-ritchie, 1986; Duchateau and Hainut, 2003) suggested that group III and IV afferents, which are stimulated by metabolites, decreases the motor unit firing rates. However, in contrast to those studies, some recent studies have shown that group III and IV afferents do not necessarily decrease voluntary activation after 2 min

MVC with elbow flexor muscles (Taylor 2000). It has been reported that group III and IV afferents depressed the excitability of extensor motor neuron while facilitated flexor motor neuron (Martin 2006). Though no measures to quantify central fatigue were taken in this study, no significant difference in firing patterns observed in this study suggest that group III and IV afferents may not necessarily inhibit alpha motor neuron. If group III and IV afferents would have inhibited motor neuron pool, then a greater depression in motor unit firing would have been observed in ischemic condition compared to the non-ischemic condition.

In this study, the coefficient of variation increased as the fatigue time increased in both the groups (non-ischemic and ischemic conditions). There was a gradual increase in coefficient of variation from 70% of endurance time compared to the initial level. Though there was a late increase in coefficient of variation in ischemic condition (from 85% of endurance time), the change was sharp. Also, the coefficient of variation was higher in ischemic group compared to non-ischemic condition at the final stage of fatigue. These findings are consistent with results of the study which found an increase in discharge variability in motor units behavior for masseter muscle during prolong submaximal contractions (Nordstrom and Miles 1991). An increase in discharge variability suggests that fatigue leads to alternations in synaptic input to the motor neuron pool or an adaptation of intrinsic motorneuron properties (Garland et al. 1994). An increase in discharge variability could also optimize force production in line with muscle wisdom (Christova and Kossev 1997). An increased variability of the motor unit interspike intervals have been observed in first dorsal interosseous (Enoka et al. 1989), biceps brachii (Garland et al. 1994), thenar muscles (Gatev 1986).

CHAPTER V: Conclusions

In conclusion, the results of this study demonstrate that muscle ischemia significantly reduced endurance time and the time to minimum firing rate. Motor unit firing rates decreased during sustained submaximal fatiguing contractions. However, there were no differences in average motor unit firing rates between the two conditions across the relative phases of endurance time. Furthermore, the discharge variability increased as the fatigue set in indicating more varying inputs to the motor neuron pool.

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